Remarks

Reconsideration of this Application is respectfully requested.

Claims 84-122 and 127-131 are pending in the application, with claims 84 and 127 being the independent claims. Claims 123-126 were previously canceled without prejudice. Applicants reserve the right to pursue the canceled subject matter in related applications. Claims 98, 100-102, and 104-106 have been withdrawn from consideration by the Examiner as reading solely on non-elected species, but remain pending.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Interview Summary

Applicants would like to thank Examiners Epperson and Celsa for the courtesy of a personal interview of May 24, 2005, at which the rejections of record and the Rowlands, Zauderer, and Waterhouse references were discussed.

Rejections under 35 U.S.C. § 112

The rejections under 35 U.S.C. § 112, first paragraph, are withdrawn. Office Action at page 2.

Rejections under 35 U.S.C. § 103

The rejection of claims 84, 88-97, 99, 103, 107-122, and 127-131 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Rowlands *et al.*, WO 93/01296

(hereinafter "Rowlands"), Zauderer, WO 00/28016 (hereinafter "Zauderer"), and Waterhouse *et al.*, *Nuc. Acids Res.* 21: 2265-66 (1993) (hereinafter "Waterhouse") was maintained. Office Action at page 3. Applicants respectfully traverse this rejection.

In particular, the Examiner asserted that:

> It would have been obvious to one skilled in the art at the time the invention was made to make a library of vaccinia virus vectors as taught by Zauderer et al. to express fully functional antibodies as taught by Rowlands et al. for the purpose of screening and/or affinity maturation as taught by Waterhouse et al. because Zauderer et al. explicitly state that their libraries can be efficiently produced using the tri-molecular recombination approach with the vaccinia virus vectors (like the vaccinia virus vectors disclosed by Rowlands et al.) and Waterhouse et al. teach that such a library would be useful in screening and affinity maturation. Applicants respectfully disagree with these assertions.

Office Action at page 8.

Section 2143 of the M.P.E.P. sets forth the basic requirements for a *prima facie* showing of obviousness:

> First, there must be some suggestion or motivation, whether in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference. . . must teach or suggest all the claim limitations.

The M.P.E.P further states that "[t]he teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure." *Id.* Applicants respectfully assert that the Examiner has not met these requirements to establish a *prima facie* case of obviousness.

First, the combination of Rowlands, Zauderer, and Waterhouse does not teach or suggest all of the limitations of the claims. In particular, the cited references do not teach or suggest the introduction of <u>two</u> expression libraries into <u>eukaryotic</u> host cells.

Rowlands discloses the introduction of vaccinia virus expression vectors containing the heavy and light chain sequences of a single, previously known and identified antibody, Campath-1H. Zauderer discloses the introduction of one library expressing tumor, cancer, or infected cell-specific antigens. Waterhouse discloses the introduction into bacterial host cells of bacteriophage vectors encoding immunoglobulin heavy and light chain variable region fragments that can undergo Cre-*lox* regulated site-specific recombination, and suggests that the system can be used to generate large combinatorial libraries by providing repertoires of heavy and light chain fragments.

Second, Applicants respectfully maintain that there was no suggestion or motivation to combine Rowlands, Zauderer, and Waterhouse to arrive at the claimed invention. The Examiner contended that:

> . . . one of ordinary skill in the art would have been motivated to make the libraries as taught by Zauderer et al. using the heavy/light chain antibodies as disclosed by Rowlands et al. because Zauderer et al. explicitly state that the [sic] their "tri-molecular" approach represents and easy and efficient means for generating a library in vaccinia virus vectors in mammalian cells, which is a preferred embodiment for Rowlands et al. . . . In addition, Waterhouse et al. teach that "associated" light and heavy chains are a "preferred" embodiment for screening and/or affinity maturation because they can be "simultaneously co-selected" . . ., which would encompass the "associated" heavy/light chains described by Rowlands et al.

Office Action at pages 8-9 (internal citations omitted). There are also repeated contentions throughout the Office Action that "Applicants' [previous] response fails to appreciate the combined teachings of 'all' the references." *See* Office Action at pages 12-16. Applicants respectfully disagree with these contentions and remind the Examiner that "[t]he mere fact that references <u>can</u> be combined or modified does not render the resultant combination obvious unless the prior art also suggests the *desirability* of the

combination." M.P.E.P. § 2143.01, p. 2100-131, 1st column (Rev. 2, May 2004) (citing *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990) (underline in original) (italics added).

There is nothing in Rowlands, Zauderer, or Waterhouse that would have motivated or suggested to one of ordinary skill in the art the desirability of combining these references. While Rowlands describes the expression of a single, previously known and identified recombinant antibody using a vaccinia virus vector, there is no suggestion provided therein that would have motivated one of ordinary skill in the art to introduce two expression libraries encoding immunoglobulin subunit polypeptides into eukaryotic cells. Furthermore, while Zauderer describes the introduction of a single expression library of tumor, cancer, or infected cell-specific antigens, there is no suggestion to one of ordinary skill in the art that this could be used in conjunction with the Rowlands method of making a single known antibody to introduce two expression libraries encoding immunoglobulin subunit polypeptides and select a previously unknown antibody as in the present invention.

Finally, Waterhouse does not even describe eukaryotic host cells; rather, Waterhouse suggests the generation of large bacteriophage antibody repertoires and subsequent infection into *bacterial hosts* for phage display. Phage display requires that the immunoglobulins be presented as fragments on the surface of a bacteriophage. The selection of a bacteriophage which carries an antigen-specific fragment is not performed in eukaryotic cells. Thus, although Waterhouse may suggest the introduction of separate repertoires of heavy and light chain variable region fragments, there is nothing in Waterhouse to suggest to one of ordinary skill in the art to introduce two expression

libraries into eukaryotic cells for selecting polynucleotides which encode an immunoglobulin molecule or a fragment thereof, as in the present invention. There is no basis for concluding that an invention would have been obvious solely because it is a combination of elements that were known in the art at the time of the invention. *See Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1556 (Fed. Cir. 1995). Since there is no suggestion or motivation to combine Rowlands, Zauderer, and Waterhouse, they cannot properly be combined to render the claimed invention obvious.

In support of Applicants' arguments, Applicants submit herewith as Exhibit B the Declaration under 37 C.F.R. § 1.132 of Dr. Maurice Zauderer. Dr. Zauderer, a co-inventor of the present application, is currently the President and Chief Executive Officer of Vaccinex, Inc., in Rochester, New York. As evidenced by his *curriculum vitae,* attached to his Declaration as Exhibit B1, Dr. Zauderer is an expert in the fields of immunology and cell biology. Dr. Zauderer provides his opinion that there was no motivation or suggestion for one of ordinary skill in the art to combine Rowlands, Zauderer, or Waterhouse to arrive at the claimed invention because: 1) Rowlands does not teach or suggest introduction of libraries into eukaryotic cells; 2) Zauderer does not teach or suggest introduction into eukaryotic host cells of two expression libraries that separately encode immunoglobulin heavy and light chains; and 3) Waterhouse describes phage display techniques, which one of ordinary skill in the art would not have considered as features that could be extrapolated to eukaryotic systems. *See* Exhibit B at Paragraph 15.

Even assuming, *arguendo*, that one of ordinary skill in the art would have been motivated to combine Rowlands, Zauderer, and Waterhouse, there would not have been a reasonable expectation of success in doing so to arrive at the present invention. The

Examiner contends that "Zauderer et al. teach several successful examples of library formation using the same vaccinia virus vectors that are disclosed by Rowlands et al. and Waterhouse et al. teach several successful examples of associated light/heavy chains that can be used for screening and/or antibody maturation, which would encompass the heavy/light chain antibodies disclosed by Rowlands et al." Office Action at page 9. Applicants respectfully disagree with the Examiner's contentions.

One of ordinary skill in the art would not have reasonably expected that the phage display technology described in Waterhouse could be extrapolated to methods of introducing two random expression libraries into eukaryotic host cells for selecting a previously unknown immunoglobulin as in the present invention. As stated above, Waterhouse describes the generation of a phage library, which involves the use of filamentous bacteriophage as a vector and bacterial cells as hosts, and the immunoglobulin fragments expressed in phage display must form part of a fusion protein with a phage protein. In contrast, the vaccinia virus vectors used in Rowlands and Zauderer are derived from an animal virus and are introduced into eukaryotic host cells for expression. Given these different vectors and the difference in prokaryotic versus eukaryotic host cells, one of ordinary skill in the art would not have expected any selection methods described in Waterhouse to be useable with vectors that express in eukaryotic hosts because there would be different conditions required for the two systems.

In fact, the present specification distinguished phage display methods because it suffers from many drawbacks as compared to the present invention (See Specification, paragraph [0008]) ("Since phage display methods normally only result in the expression of an antigen-binding fragment of an immunoglobulin molecule, after phage selection,

the immunoglobulin coding regions from the phage must be isolated to generate whole antibodies, including human antibodies, or any other desired antigen binding fragment, and expressed in any desired host cell including mammalian cells, insect cells, plant cells, yeast, and bacteria.")) Thus, an immunoglobulin fragment of interest would have to be identified and selected in a prokaryotic system by phage display, then re-cloned into a eukaryotic expression vector in order to be expressed in a eukaryotic host cell. Advantageously, this extra step is not required by the methods of the present invention.

Furthermore, one of ordinary skill in the art would not have expected from Zauderer, which discloses introduction of one library into eukaryotic host cells, and Rowlands, which discloses the expression of a previously identified and known antibody in eukaryotic cells, that two separate libraries could be randomly introduced into eukaryotic host cells to efficiently form a plurality of immunoglobulin molecules from which an immunoglobulin molecule of interest could be identified and selected. Therefore, absent a reasonable expectation of success, the cited references cannot properly be combined to render the claimed invention obvious.

In further support of Applicants' arguments, Applicants submit herewith as Exhibit A the Declaration under 37 C.F.R. § 1.132 of Dr. Walter J. Storkus. As evidenced by his *curriculum vitae,* attached to his Declaration as Exhibit A1, Dr. Storkus is currently a tenured professor in the Departments of Immunology and Dermatology at the University of Pittsburgh, and is an expert in the field of immunology. Dr. Storkus has provided his opinion that, when the idea of an antibody selection system using two separate random libraries of eukaryotic expression vectors to identify immunoglobulins of interest as disclosed in the '456 application was first proposed to him as a member of the Scientific Advisory Board (SAB) of Vaccinex, Inc., he was skeptical that the

technology would work to select antigen-specific immunoglobulins. *See* Exhibit A at Paragraph 6. In particular, Dr. Storkus states that he did not expect that good antibodies could be selected in eukaryotic cells because, *inter alia*, he thought that there would be limitations on the throughput for screening libraries expressed in eukaryotic cells, and because it was thought that random pairs of immunoglobulin heavy and light chains, when expressed, would not associate properly in the eukaryotic cytoplasm. *Id.* at Paragraph 7. Dr. Storkus also indicates that his expectations for the success of the claimed invention would not have changed in view of Rowlands, Zauderer, and Waterhouse. *See* Exhibit B at Paragraph 9.

Finally, even if the cited references could be properly combined (which they cannot) and disclosed all of the elements of the presently claimed invention (which they do not), it is well-established that a *prima facie* case of obviousness can be overcome by a showing of objective indicia of non-obviousness such as a long-felt and unmet need, failed attempts by others, commercial success, and unexpected results. *See e.g., Graham v. John Deere Co.*, 86 S.Ct. 684, 694 (1966); *Custom Accessories v. Jeffrey-Allan Industries*, 807 F.2d 955, 960 (Fed. Cir. 1986); *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). In his Declaration, Dr. Zauderer provides his opinion that there was a long-felt and unmet need for the technology of the claimed invention because of the drawbacks that are associated with the two prevalent technologies for selecting human antibodies. Exhibit B at Paragraphs 16-17. This long felt need is evidenced by the strategic alliances that have been formed between Vaccinex, Inc., exclusive licensee of the present invention, and several other companies that are interested in using the claimed invention. *Id.* at Paragraph 18.

Since there was no suggestion or motivation to combine Rowlands, Zauderer, or Waterhouse, and no reasonable expectation of success from the combination, a *prima facie* case of obviousness is not established. Furthermore, there was clearly a long felt need for the claimed invention. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection Based on Non-Statutory Obviousness-Type Double Patenting

In the Office Action at pages 23-24, the Examiner has provisionally rejected claims 84, 88-97, 99, 103, 107-122, and 127-131, for alleged obviousness-type double patenting over claims 1-84 of commonly-owned U.S. Patent Application Publication No. 2003/0104402 A1 ("the '402 publication") in view of Rowlands. Applicants respectfully request that this rejection be held in abeyance until such time as otherwise patentable subject matter has been identified in either the present application or the '402 publication. At that time, Applicants will consider filing a terminal disclaimer.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Reply is respectfully requested.

Respectfully submitted,

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